Open Forum Infectious Diseases

MAJOR ARTICLE

Risk Factors for Candidemia After Open Heart Surgery: Results From a Multicenter Case–Control Study

Daniele Roberto Giacobbe,[1,2,a] Antonio Salsano,[3,4,a] Filippo Del Puente,[1] Ambra Miette,[3,4] Antonio Vena,[1,2] Silvia Corcione,[5] Michele Bartoletti,[6] Alessandra Mularoni,[7] Alberto Enrico Maraolo,[8] Maddalena Peghin,[9] Alessia Carnelutti,[9] Angela Raffaella Losito,[10] Francesca Raffaelli,[10] Ivan Gentile,[8] Beatrice Maccari,[11] Stefano Frisone,[11] Renato Pascale,[6] Elisa Mikus,[12] Alice Annalisa Medaglia,[7] Elena Conoscenti,[7] Davide Ricci,[4] Tommaso Lupia,[5] Marco Comaschi,[11] Maddalena Giannella,[6] Mario Tumbarello,[10] Francesco Giuseppe De Rosa,[5] Valerio Del Bono,[13] Malgorzata Mikulska,[1,2] Francesco Santini,[3,4] and Matteo Bassetti[1,2]; on behalf of SITA GIOVANI (Young Investigators of the Italian Society of Anti-infective Therapy)

[1]Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy, [2]Clinica Malattie Infettive, Ospedale Policlinico San Martino - IRCCS, Genoa, Italy, [3]Department of Integrated Surgical and Diagnostic Sciences (DISC), University of Genoa, Genoa, Italy, [4]Division of Cardiac Surgery, Ospedale Policlinico San Martino - IRCCS, Genoa, Italy, [5]Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy, [6]Department of Medical and Surgical Sciences, Infectious Diseases Unit, Alma Mater Studiorum-University of Bologna, Bologna, Italy, [7]Infectious Diseases ISMETT IRCCS, Palermo, Italy, [8]Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy, [9]Department of Medicine, University of Udine and Azienda Sanitaria Universitaria Integrata, Udine, Italy, [10]Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, [11]ICLAS - GVM Care & Research, Rapallo, Italy, [12]Maria Cecilia Hospital - GVM Care & Research, Cotignola, Italy, and [13]Infectious Diseases Unit, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy

Background. *Candida* species are among the most frequent causative agents of health care–associated bloodstream infections, with mortality >40% in critically ill patients. Specific populations of critically ill patients may present peculiar risk factors related to their reason for intensive care unit admission. The primary objective of the present study was to assess the predictors of candidemia after open heart surgery.

Methods. This retrospective, matched case–control study was conducted in 8 Italian hospitals from 2009 to 2016. The primary study objective was to assess factors associated with the development of candidemia after open heart surgery.

Results. Overall, 222 patients (74 cases and 148 controls) were included in the study. Candidemia developed at a median time (interquartile range) of 23 (14–36) days after surgery. In multivariable analysis, independent predictors of candidemia were New York Heart Association class III or IV (odds ratio [OR], 23.81; 95% CI, 5.73–98.95; $P < .001$), previous therapy with carbapenems (OR, 8.87; 95% CI, 2.57–30.67; $P = .001$), and previous therapy with fluoroquinolones (OR, 5.73; 95% CI, 1.61–20.41; $P = .007$). Crude 30-day mortality of candidemia was 53% (39/74). Septic shock was independently associated with mortality in the multivariable model (OR, 5.64; 95% CI, 1.91–16.63; $P = .002$). No association between prolonged cardiopulmonary bypass time and candidemia was observed in this study.

Conclusions. Previous broad-spectrum antibiotic therapy and high NYHA class were independent predictors of candidemia in cardiac surgery patients with prolonged postoperative intensive care unit stay.

Keywords. bloodstream infection; *Candida*; cardiac surgery; postoperative complications.

In modern hospitals, many open heart surgical interventions are performed every day. Although cardiac surgery techniques have improved considerably over the last few years, a wide array of systemic and local infectious complications associated with these procedures have been reported [1, 2]. They are mainly local complications (eg, sternal wound infections), and overall bacterial etiology predominates [3, 4]. However, patients undergoing open heart surgery may also develop *Candida* bloodstream infections [5, 6].

Candida bloodstream infection (candidemia) has been associated with increased morbidity and mortality in critically ill patients [7–19], and various general risk factors (eg, administration of broad-spectrum antibiotics, prolonged length of hospital stay, presence of a central venous catheter) have been extensively characterized [20–23]. Nonetheless, specific populations of critically ill patients may present additional peculiar risk factors related to their medical or surgical reasons for intensive care unit (ICU) admission [6, 23–27]. Therefore, we conducted a case–control study in 8 hospitals in Italy to assess the predictors of candidemia after open heart surgery.

METHODS

Study Design and Objectives

The present observational, retrospective case–control study was conducted in 8 Italian centers located in 7 different

Received 12 February 2020; editorial decision 8 June 2020; accepted 11 June 2020.

[a]Equal contribution.

Correspondence: Daniele Roberto Giacobbe, Clinica Malattie Infettive, Ospedale Policlinico San Martino - IRCCS, L.go R. Benzi 10, 16132 Genoa, Italy (daniele.roberto.giacobbe@gmail.com).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofaa233

Italian regions. The study period was from January 1, 2009, to December 31, 2016. All patients who developed candidemia during the study period and during the ICU stay after open heart surgery were included as cases. Two controls without candidemia were matched to each case by the following criteria: (i) center; (ii) date of open heart surgery (±1 month); (iii) time at risk. For cases, time at risk was defined as the number of days elapsed from surgery to the onset of candidemia (ie, the day when the first blood culture positive for *Candida* spp. was drawn). For controls, time at risk was defined as the number of days elapsed from surgery to hospital discharge or in-hospital death. To avoid scarce fulfillment of the matching criterion, we arbitrarily set the time at risk in controls to be equal to or longer than the time at risk in cases minus 5 days. Cases were included in the study only once, at the time of the first episode of candidemia after open heart surgery.

The primary study objective was to assess factors associated with the development of postoperative candidemia. The assessment of predictors of crude mortality within 30 days after the onset of candidemia in cases was a secondary study objective. The study was approved by the ethical committee of the coordinating center (Ethical Committee of Liguria Region, registry number 320REG2017). The other participating centers followed the local ethical requirements.

Data Collection

The following baseline data (preoperative and peri/intraoperative variables) were retrospectively collected from medical records and laboratory databases of the participating hospitals: age, gender, diabetes (defined as any preoperative diagnosis of diabetes mellitus requiring treatment), New York Heart Association (NYHA) class of heart failure, preoperative serum creatinine >200 μmol/L, chronic obstructive pulmonary disease (COPD; defined as long-term use of bronchodilators or steroids for lung disease), history of immunosuppression (defined as 1 or more of the following: solid organ transplantation, malignancy, neutropenia [absolute neutrophil count <1000 cells/mm^3], HIV infection, chemotherapy within 45 days before surgery, therapy with ≥10 mg of prednisone or its equivalent per day for >14 days before surgery), Charlson Comorbidity Index [28], peripheral vascular disease (defined as ≥1 of the following: carotid occlusion or >50% stenosis, claudication, amputation for arterial disease, previous or planned intervention on the abdominal aorta, carotids, or limb arteries), preoperative stroke (defined as any focal or global neurological syndrome caused by ischemia or hemorrhage not resolving within 24 hours), previous acute myocardial infarction (within 3 months), left ventricular ejection fraction (LVEF), EuroSCORE II [29], type of open heart surgery (categorized as isolated coronary artery bypass surgery, isolated valvular surgery, surgery of thoracic aorta, or other/combined procedures), preoperative mechanical ventilation, pacemaker implantation, cardiopulmonary bypass (CPB) time in minutes, aortic cross-clamp time in minutes, sequential organ failure assessment (SOFA) score at the time of surgery [30], need for peri/intraoperative blood transfusions.

The following data were also collected over the duration of the time at risk for candidemia in both cases and controls (postoperative variables): presence of central venous catheter for >48 hours, receipt of total parenteral nutrition for >48 hours, hemodialysis therapy for >48 hours, administration of broad-spectrum antibiotics for >48 hours, *Candida* colonization (defined as isolation of *Candida* spp. from nonsterile sites in absence of signs and symptoms of infection), bacterial bloodstream infections (defined as isolation of bacteria from blood in presence of signs and symptoms of infections, at least 2 positive cultures were required for coagulase-negative staphylococci).

The following data were also collected for cases (candidemia-related variables): species of *Candida* isolated from blood, presence of septic shock at the time of candidemia (according to Sepsis-3 criteria [31]), removal of central venous catheter within 48 hours after the onset of candidemia, administration of antifungal therapy within 48 hours after the onset of candidemia.

Microbiology

Candida spp. were identified using the VITEK 2 automated system (bioMérieux, Marcy l'Etoile, France) or by MALDI-TOF mass spectrometry (bioMérieux, Marcy l'Etoile, France, or Bruker Daltonik, Bremen, Germany), according to the standard laboratory diagnostic procedures adopted in the different participating centers.

Statistical Analysis

The primary study analysis was the identification of factors associated with the development of candidemia after open heart surgery. To this aim, demographic and clinical variables were first tested for their association with the dependent variable (development of candidemia) in univariable conditional logistic regression models for matched pairs/sets, with strata composed by sets of single cases and their 2 matched controls [32]. Then, variables associated with the development of candidemia in univariable comparisons ($P < .05$) were included in an initial multivariable, conditional logistic regression model for matched pairs/sets and further selected for the final multivariable model by means of a stepwise backward procedure. A secondary study analysis was the identification of factors associated with crude 30-day mortality in candidemia cases. To this aim, we employed univariable and multivariable comparisons as for the primary analysis, with the exception of using unconditional logistic regression models. The analyses were performed using SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Overall, 222 patients were included in the study (74 cases and 148 controls). Strict application of matching criteria was possible for 56% of controls (83/148). Owing to the absence of other controls fulfilling all 3 matching criteria, the remaining 44% (65/148) were selected as those with the nearest date of surgery (with respect to cases) outside the matching period (ie, beyond ± 1 month) but still fulfilling the matching criteria for center and time at risk.

During the study period, 36 476 open heart surgery procedures were performed in the participating centers. The cumulative incidence of postoperative candidemia over the study period was of 2.03 episodes per 1000 open heart surgery patients. The median age of patients with candidemia (interquartile range [IQR]) was 72 (64–78) years, and 55% were males. The median time to development of candidemia (IQR) was 23 (14–36) days after surgery. Concomitant *Candida* endophthalmitis was diagnosed in 1% of cases (1/74). No concomitant *Candida* endocarditis was observed. Most candidemia episodes were due to *C. albicans* (48/74, 65%), followed by *C. parapsilosis* (10/74, 14%) and *C. glabrata* (7/74, 9%).

Table 1 shows the results of univariable and multivariable analyses of factors associated with the development of candidemia. In univariable analysis, NYHA class III or IV, previous stroke, low LVEF, higher EuroSCORE II score, preoperative mechanical ventilation, hemodialysis therapy, SOFA score at the time of surgery, previous therapy with cephalosporins, previous therapy with carbapenems, previous therapy with fluoroquinolones, and multifocal *Candida* colonization had a statistically significant association with the development of candidemia. In the final multivariable model, NYHA class III or IV (odds ratio [OR], 23.81; 95% CI, 5.73–98.95; $P < .001$), previous therapy with carbapenems (OR, 8.87; 95% CI, 2.57–30.67; $P = .001$), and previous therapy with fluoroquinolones (OR, 5.73; 95% CI, 1.61–20.41; $P = .007$) retained an independent association.

Thirty-day crude mortality in patients with candidemia was 53% (39/74), whereas the crude in-hospital mortality of controls was 15% (22/148; chi-square test, $P < .001$). The results of univariable and multivariable analyses of factors associated with 30-day mortality in patients with candidemia are shown in Table 2. In univariable analysis, >5 peri/intraoperative blood transfusions, previous therapy with fluoroquinolones, and septic shock at the onset of candidemia were associated with increased 30-day mortality. Only septic shock, observed in as many as 36% of patients with candidemia, retained an independent association with the outcome in the final multivariable model (OR, 5.64; 95% CI, 1.91–16.63; $P = .002$).

DISCUSSION

In this retrospective, multicenter, case–control study, high NYHA class, previous therapy with carbapenems, and previous therapy with fluoroquinolones were associated with the development of candidemia after open heart surgery.

Risk factors for developing candidemia after open heart surgery have also been explored by other studies. Michalopoulos and colleagues conducted a single-center, case–control study in 150 cardiac surgery patients (30 cases with postoperative candidemia and 120 controls without candidemia) [24]. Controls were matched to cases according to gender, body mass index, agents administered for general anesthesia and for postoperative sedation, type of employed cardioplegia, and CPB technique. Independent predictors of candidemia were mechanical ventilation >10 days, hospital-acquired bacterial infection and/or bacteremia, CPB time >120 minutes, and diabetes mellitus [24]. Subsequently, Pasero and colleagues assessed risk factors for candidemia in a cohort of patients admitted to a cardiac surgery ICU [6]. Among 349 patients, 26 developed candidemia. Independent predictors of candidemia were ICU length of stay >20 days, total parenteral nutrition, severe sepsis, and high simplified acute physiology score (SAPS II), whereas no association with development of candidemia was observed for CPB time [6].

Similar to Pasero and colleagues, we did not find an association between prolonged CPB and development of postoperative candidemia (thus apparently not being in line with the hypothesis of an enhanced intestinal permeability related to prolonged CPB-related ischemia, with possible increased risk of translocation of bacteria and/or fungi from the intestinal lumen to the bloodstream) [33–35]. In the interpretation of this results, it should be kept in mind that in our study we focused on a subpopulation of cardiac surgery patients (ie, those with prolonged postoperative ICU stay). Indeed, candidemia mostly developed late during ICU stay (and thus the length of postoperative ICU stay was inherently long, also in matched controls), a fact that is in line with the well-known role of prolonged hospital stay as a general predictor of candidemia [5, 6, 20, 23, 24]. Overall, this may suggest that CPB time is not helpful for discriminating the risk of candidemia (absolutely or vs that of bacterial BSI [35]) in cardiac surgery patients with prolonged ICU stay, that is, in those who usually are the most likely to develop candidemia because they already express classical, non-surgery-related risk factors. For example, our results confirm that the previous administration of broad-spectrum antibiotics is an important risk factor for candidemia in cardiac surgery patients, in line with the results of previous studies conducted in more general populations [20, 22, 23, 36–38], and potentially explained by the disruptive effect that previous broad-spectrum antibiotics may have on the human microbiota with consequent increased risk of *Candida* translocation [39]. In addition, we found a high baseline NYHA class

Table 1. Univariable and Multivariable Analyses of Factors Associated With the Development of Candidemia After Open Heart Surgery

Variable	No. of Cases (%) 74 (100)	No. of Controls (%) 148 (100)	Univariable Analysis Odds Ratio (95% CI)	*P*	Multivariable Analysis[a] Odds Ratio (95% CI)	*P*
Preoperative and peri/intraoperative variables						
Age, median (IQR), y	72 (64–78)	72 (64–77)	1.00 (0.98–1.03)	.932		
Male gender	41 (55)	99 (67)	0.64 (0.37–1.11)	.113		
Diabetes mellitus	23 (31)	29 (20)	1.80 (0.96–3.39)	.067		
NYHA class III/IV	53 (72)	40 (27)	6.26 (3.21–12.21)	<.001	23.81 (5.73–98.95)	<.001
Preoperative serum creatinine >200 μmol/L	29 (39)	42 (28)	1.63 (0.90–2.95)	.105		
COPD	22 (30)	36 (24)	1.34 (0.70–2.56)	.372		
History of immunosuppression	1 (1)	9 (6)	0.20 (0.02–1.64)	.133		
Charlson Comorbidity Index, median (IQR)	5 (3–7)	5 (3–6)	1.08 (0.95–1.23)	.232		
Peripheral vascular disease	14 (19)	27 (18)	1.04 (0.52–2.10)	.905		
Previous stroke	12 (16)	8 (5)	4.00 (1.38–11.57)	.010	4.61 (0.68–31.28)	.118
Previous IMA	13 (18)	31 (21)	0.83 (0.42–1.62)	.577		
LVEF, median (IQR), %	50 (37–55)	55 (45–55)	0.97 (0.95–1.00)	.031	-	.633
EuroSCORE II	6.61 (3.67–16.43)	3.51 (1.86–8.37)	1.06 (1.02–1.10)	.001	-	.177
Preoperative MV	16 (22)	9 (6)	3.56 (1.57–8.05)	.002	-	.275
Type of surgery				.073		
Isolated coronary artery bypass surgery	6 (8)	22 (15)	(ref)			
Isolated valvular surgery	32 (43)	48 (32)	2.43 (0.88–6.71)			
Surgery of thoracic aorta	26 (35)	41 (28)	2.13 (0.78–5.82)			
Other/combined procedures	10 (14)	37 (25)	0.93 (0.29–2.97)			
Pacemaker implantation	2 (3)	10 (7)	0.40 (0.09–1.83)	.237		
CPB time, median (IQR), min	136 (98–208)	136 (92–197)	1.00 (1.00-1.00)	.843		
Aortic cross-clamp time, median (IQR), min	75 (49–120)	87 (58–120)	1.00 (0.99–1.00)	.127		
SOFA score at time of surgery, median (IQR)	4 (1–7)	3 (0–4)	1.19 (1.07–1.34)	.002	1.20 (0.99–1.45)	.058
Need for peri/intraoperative blood transfusion	61 (82)	124 (84)	0.85 (0.33–2.22)	.854		
Need for >5 peri/intraoperative blood transfusions	47 (64)	86 (58)	1.56 (0.69–3.52)	.288		
Postoperative (during time at risk)						
Central venous catheter >48 h	74 (100)	141 (95)	(model not converging)	-		
Total parenteral nutrition >48 h	42 (57)	86 (58)	0.94 (0.50–1.74)	.833		
Hemodialysis >48 h	27 (37)	28 (19)	2.55 (1.32–4.91)	.005	-	.566
Therapy with cephalosporins >48 h	18 (24)	12 (8)	4.65 (1.81–11.94)	.001	-	-
Therapy with carbapenems >48 h	52 (70)	51 (35)	4.49 (2.37–8.49)	<.001	8.87 (2.57–30.67)	.001
Therapy with fluoroquinolones >48 h	49 (66)	51 (35)	5.78 (2.64–12.65)	<.001	5.73 (1.61–20.41)	.007
Candida colonization	29 (39)	45 (30)	1.52 (0.83–2.80)	.178		
Candida multifocal colonization (at least 2 sites)	19 (26)	14 (10)	2.95 (1.43–6.12)	.004	-	.723
Bacterial BSI[b]	23 (31)	38 (26)	1.30 (0.69–2.47)	.415		

Results are presented as No. (%) unless otherwise indicated.

Abbreviations: BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; IMA, acute myocardial infarction; IQR, interquartile range; LVEF, left ventricular ejection fraction; MV, mechanical ventilation; NYHA, New York Hearth Association.

[a]Odds ratio and 95% CI are presented only for variables retained in the final multivariable model (ie, NYHA class III/IV, previous stroke, SOFA score at time of surgery, therapy with fluoroquinolones >48 hours, therapy with carbapenems >48 hours).

[b]Coagulase-negative staphylococci (n = 24), *Klebsiella* spp. (n = 8), *Staphylococcus aureus* (n = 6), *Enterobacter* spp. (n = 3), *Pseudomonas* spp. (n = 3), *Enterococcus* spp. (n = 2), and other bacteria with lower frequencies (n = 15).

to be an independent predictor of postoperative candidemia. This finding warrants further investigation, as this predisposing factor was not investigated in other studies assessing predictors of candidemia in cardiac surgery patients. However, it remains reasonable that a high NYHA class may represent a proxy for a higher burden of comorbidity or need for more intensive care procedures, possibly and generally influencing the risk of postoperative infections.

As a secondary analysis, we assessed the predictors of 30-day mortality in patients with postoperative candidemia. In this regard, the independent association we observed between septic shock and mortality further confirms the importance of the severity of clinical presentation in unfavorably influencing the outcome [17]. On the other hand, caution is needed before interpreting the absence of other independent predictors of mortality in our analysis. For example, early antifungal therapy and early CVC removal have been previously indicated as important predictors of survival [7, 40], and it is worth noting that a trend toward improved survival for these 2 factors was also appreciable in our univariable results, although it did

Table 2. Univariable and Multivariable Analyses of Factors Associated With 30-Day Mortality in Open Heart Surgery Patients With Postoperative Candidemia

Variable	Nonsurvivors, No. (%) 39 (100)	Survivors, No. (%) 35 (100)	Univariable Analysis Odds Ratio (95% CI)	*P*	Multivariable Analysis[b] Odds Ratio (95% CI)	*P*
Preoperative and peri/intraoperative variables						
Age, median (IQR), y	75 (67–79)	68 (60–76)	1.03 (0.99–1.08)	.129		
Male gender	21 (54)	20 (57)	0.88 (0.35–2.19)	.776		
Diabetes mellitus	11 (28)	12 (34)	0.75 (0.28–2.02)	.573		
NYHA class III/IV	29 (74)	24 (69)	1.33 (0.48–3.66)	.582		
Preoperative serum creatinine >200 μmol/L	17 (44)	12 (34)	1.48 (0.58–3.80)	.414		
COPD	12 (31)	10 (29)	1.11 (0.41–3.02)	.836		
History of immunosuppression	1 (3)	0 (0)	(model not converging)	-		
Charlson Comorbidity Index, median (IQR)	5 (3–7)	5 (2–6)	1.09 (0.90–1.32)	.390		
Peripheral vascular disease	7 (18)	7 (20)	0.88 (0.27–2.80)	.822		
Previous stroke	7 (18)	5 (14)	1.31 (0.38–4.59)	.670		
Previous IMA	10 (26)	3 (9)	3.68 (0.92–14.69)	.065		
LVEF, median (IQR), %	50 (35–55)	48 (39–55)	1.00 (0.96–1.04)	.984		
EuroSCORE II	13.57 (4.07–21.93)	4.57 (3.43–10.34)	1.05 (1.00–1.10)	.052		
Preoperative MV	10 (26)	6 (17)	1.67 (0.54–5.19)	.378		
Type of surgery				.898		
Isolated coronary artery bypass surgery	4 (10)	2 (6)	(ref)			
Isolated valvular surgery	16 (41)	16 (46)	0.50 (0.08–3.13)			
Surgery of thoracic aorta	14 (36)	12 (34)	0.58 (0.09–3.76)			
Other/combined procedures	5 (13)	5 (14)	0.50 (0.06–4.09)			
Pacemaker implantation	1 (3)	1 (3)	0.90 (0.05–14.86)	.938		
CPB time, median (IQR), min	136 (98–198)	137 (93–213)	1.00 (1.00-1.00)	.652		
Aortic cross-clamp time, median (IQR), min	73 (51–110)	89 (49–140)	1.00 (0.99–1.01)	.603		
SOFA score at time of surgery, median (IQR)	4 (1–7)	3 (1–6)	1.02 (0.89–1.17)	.749		
Need for peri/intraoperative blood transfusion	32 (82)	29 (83)	0.95 (0.29–3.14)	.928		
Need for >5 peri/intraoperative blood transfusions	29 (74)	18 (51)	2.74 (1.03–7.28)	.043	-	.151
Postoperative variables (during time at risk)						
Central venous catheter >48 h	39 (100)	35 (100)	-	-		
Total parenteral nutrition >48 h	25 (64)	17 (49)	1.89 (0.75–4.80)	.180		
Hemodialysis >48 h	16 (41)	11 (31)	1.52 (0.58–3.95)	.393		
Therapy with cephalosporins >48 h	10 (26)	8 (23)	1.16 (0.40–3.38)	.781		
Therapy with carbapenems >48 h	26 (67)	26 (74)	0.69 (0.25–1.90)	.475		
Therapy with fluoroquinolones >48 h	30 (77)	19 (54)	2.81 (1.03–7.62)	.043	-	.115
Candida colonization	13 (33)	16 (46)	0.59 (0.23–1.52)	.278		
Candida multifocal colonization (≥2 sites)	9 (23)	10 (29)	0.75 (0.26–2.13)	.590		
Bacterial BSI[b]	9 (23)	14 (40)	0.45 (0.17–1.23)	.120		
Candidemia-related variables						
Septic shock	21 (54)	6 (17)	5.64 (1.91–16.63)	.002	5.64 (1.91–16.63)	.002
Causative *Candida* species				.184		
albicans	28 (74)	20 (59)	(ref)			
Non-*albicans*[c]	10 (26)	14 (41)	0.51 (0.19–1.38)			
Early antifungal therapy (within 48 h[d])	13 (33)	16 (46)	0.59 (0.23–1.52)	.278		
Early CVC removal (within 48 h[d])	13 (33)	14 (40)	0.75 (0.29–1.94)	.552		

Results are presented as No. (%) unless otherwise indicated.

Abbreviations: BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVC, central venous catheter; IMA, acute myocardial infarction; IQR, interquartile range; LVEF, left ventricular ejection fraction; MV, mechanical ventilation; NYHA, New York Hearth Association.

[a]Odds ratio and 95% CI are presented only for the variables retained in the final multivariable model (ie, septic shock).

[b]Coagulase-negative staphylococci (n = 8), *Klebsiella* spp. (n = 5), *Pseudomonas* spp. (n = 3), *Staphylococcus aureus* (n = 2), other bacteria with lower frequencies (n = 5).

[c]Two nontyped species were not included in the comparison *albicans* vs non-*albicans* species. Typed non-*albicans* species were as follows: *C. parapsilosis* (n = 10), *C. glabrata* (n = 7), *C. tropicalis* (n = 3), *C. krusei* (n = 2), *C. dubliniensis* (n = 1), *C. sake* (n = 1).

[d]After the onset of candidemia (ie, the day when the first positive blood culture for *Candida* spp. was drawn).

not reach statistical significance (possibly because of reduced power). Finally, it is of note that the low cumulative incidence of candidemia we found was similar to that observed in surgical ICUs in a recent European multicenter study [17], possibly reflecting the presence in the denominator of a high number of patients with short postoperative ICU stay and consequent low risk of candidemia.

This study has some important limitations. The most important are related to its retrospective nature and mainly consist of possible information biases (eg, we did not systematically register the number of performed ophthalmologist evaluations and echocardiograms in cases, although they are considered standard procedures in our centers). Another limitation is that we were unable to retrospectively collect sufficient data and/or adjustments for time at risk for some postoperative intensive care procedures (eg, use of intra-aortic balloon pump) and some postoperative noninfectious complications (eg, reoperations for bleeding) that may have influenced the risk of infection. Two other important limitations are the lack of long-term follow-up in survivors of candidemia [26] and the use of a single control group instead of 2 different control groups to separately assess (i) the predictors of candidemia vs no infection and (ii) the predictors of candidemia vs bacteremia. Finally, although increased with respect to previous studies, the power of our primary analysis remains somewhat suboptimal; thus we may have failed to detect other true associations that could be clinically relevant. Nonetheless, to our knowledge this is the largest cohort of candidemic cardiac surgery patients (n = 74) employed for assessing the risk of postoperative candidemia, and it may add valuable information to the literature, complementary to that of previous studies with more limited sample sizes.

In conclusion, previous broad-spectrum antibiotic therapy and high NYHA class were independent predictors of candidemia in cardiac surgery patients with prolonged postoperative ICU stay, whereas no association between prolonged CPB time and candidemia was observed in the present case–control study. Further studies are needed to explore the possible role of CPB-related ischemia in influencing the risk of candidemia episodes occurring early after surgery.

Acknowledgments

Financial support. None.

Potential conflicts of interest. Outside the submitted work, D.R.G. reports an unconditional grant from MSD Italia and personal fees from Stepstone Pharma GmbH. Outside the submitted work, M.B. serves on scientific advisory boards for Angelini, AstraZeneca, Bayer, Cubist, Pfizer, Menarini, MSD, Nabriva, Paratek, Roche, Shionogi, Tetraphase, The Medicine Company, and Astellas Pharma Inc.; has received funding for travel or speaker honoraria from Algorithm, Angelini, Astellas Pharma Inc., AstraZeneca, Cubist, Pfizer MSD, Gilead Sciences, Menarini, Novartis, Ranbaxy, and Teva. Outside the submitted work, I.G. reports personal fees from AbbVie, Angelini, Correvio, MSD, Nordic, and Pfizer and grants from Gilead Sciences. Outside the submitted work, M.M. has received speaker and advisory board fees from Gilead, Pfizer, Janssen, and MSD. The other authors have no conflicts of interest to disclose. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. D.R.G., A.S., M.B., F.S., and V.D.B. designed the study and critically revised the manuscript draft; D.R.G., A.S., and F.D.P. performed the statistical analysis; D.R.G. drafted the manuscript; A.S., F.D.P., A.Mi., A.V., S.C., M.B., A.Mu., A.E.M., M.P., A.C., A.R.L., F.R., I.G., B.M., S.F., R.P., E.M., A.A.M., E.C., D.R., T.L., and M.C. collected data and critically revised the manuscript draft; M.M., M.G., M.T., and F.G.D.R. critically revised the manuscript draft.

References

1. Jiang WL, Hu XP, Hu ZP, et al. Morbidity and mortality of nosocomial infection after cardiovascular surgery: a report of 1606 cases. Curr Med Sci **2018**; 38:329–35.
2. Giacobbe DR, Corcione S, Salsano A, et al. Current and emerging pharmacotherapy for the treatment of infections following open heart surgery. Expert Opin Pharmacother **2019**; 20(6):751–72.
3. Kollef MH, Sharpless L, Vlasnik J, et al. The impact of nosocomial infections on patient outcomes following cardiac surgery. Chest **1997**; 112:666–75.
4. Lemaignen A, Birgand G, Ghodhbane W, et al. Sternal wound infection after cardiac surgery: incidence and risk factors according to clinical presentation. Clin Microbiol Infect **2015**; 21:674.e11–8.
5. Michalopoulos A, Kriaras J, Geroulanos S. Systemic candidiasis in cardiac surgery patients. Eur J Cardiothorac Surg **1997**; 11:728–31.
6. Pasero D, De Rosa FG, Rana NK, et al. Candidemia after cardiac surgery in the intensive care unit: an observational study. Interact Cardiovasc Thorac Surg **2011**; 12:374–8.
7. Bassetti M, Righi E, Ansaldi F, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. Intensive Care Med **2014**; 40:839–45.
8. Bouza E, Muñoz P. Epidemiology of candidemia in intensive care units. Int J Antimicrob Agents **2008**; 32(Suppl 2):S87–91.
9. Marchetti O, Bille J, Fluckiger U, et al; Fungal Infection Network of Switzerland. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991-2000. Clin Infect Dis **2004**; 38:311–20.
10. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
11. Baldesi O, Bailly S, Ruckly S, et al; REA-RAISIN network. ICU-acquired candidaemia in France: epidemiology and temporal trends, 2004-2013 - a study from the REA-RAISIN network. J Infect **2017**; 75:59–67.
12. Bougnoux ME, Kac G, Aegerter P, et al; CandiRea Study Group. Candidemia and candiduria in critically ill patients admitted to intensive care units in France: incidence, molecular diversity, management and outcome. Intensive Care Med **2008**; 34:292–9.
13. Kett DH, Azoulay E, Echeverria PM, Vincent JL; Extended Prevalence of Infection in ICU Study (EPIC II) Group of Investigators. *Candida* bloodstream infections in intensive care units: analysis of the extended prevalence of infection in intensive care unit study. Crit Care Med **2011**; 39:665–70.
14. Klingspor L, Tortorano AM, Peman J, et al. Invasive *Candida* infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006–2008). Clin Microbiol Infect **2015**; 21:87.e1–87.e10.
15. Tortorano AM, Dho G, Prigitano A, et al; ECMM-FIMUA Study Group. Invasive fungal infections in the intensive care unit: a multicentre, prospective, observational study in Italy (2006-2008). Mycoses **2012**; 55:73–9.
16. Vincent JL, Rello J, Marshall J, et al; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. JAMA **2009**; 302:2323–9.
17. Bassetti M, Giacobbe DR, Vena A, et al. Incidence and outcome of invasive candidiasis in intensive care units (ICUs) in Europe: results of the EUCANDICU project. Crit Care **2019**; 23:219.
18. Paiva JA, Pereira JM, Tabah A, et al. Characteristics and risk factors for 28-day mortality of hospital acquired fungemias in ICUs: data from the EUROBACT study. Crit Care **2016**; 20:53.
19. Tabah A, Koulenti D, Laupland K, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med **2012**; 38: 1930–45.
20. Hermsen ED, Zapapas MK, Maiefski M, et al. Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case-control study. Crit Care **2011**; 15:R198.

21. León C, Ruiz-Santana S, Saavedra P, et al; EPCAN Study Group. A bedside scoring system ("*Candida* score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. Crit Care Med **2006**; 34:730–7.
22. Ostrosky-Zeichner L, Sable C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis **2007**; 26:271–6.
23. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. Med Mycol **2005**; 43:235–43.
24. Michalopoulos AS, Geroulanos S, Mentzelopoulos SD. Determinants of candidemia and candidemia-related death in cardiothoracic ICU patients. Chest **2003**; 124:2244–55.
25. Nieto-Rodriguez JA, Kusne S, Mañez R, et al. Factors associated with the development of candidemia and candidemia-related death among liver transplant recipients. Ann Surg **1996**; 223:70–6.
26. Russo A, Falcone M, Picciarella A, et al. Candidaemia after heart valve replacement surgery: recurrence as prosthetic valve endocarditis is an expected over one-year complication. Clin Microbiol Infect **2016**; 22:466–7.
27. van Hal SJ, Marriott DJ, Chen SC, et al; Australian Candidaemia Study. Candidemia following solid organ transplantation in the era of antifungal prophylaxis: the Australian experience. Transpl Infect Dis **2009**; 11:122–7.
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
29. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg **2012**; 41:734–44; discussion 744–5.
30. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med **1996**; 22:707–10.
31. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA **2016**; 315:801–10.
32. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd ed. Hoboken, NJ: John Wiley and Sons, Inc.; **2013**.
33. Feltis BA, Wells CL. Does microbial translocation play a role in critical illness? Curr Opin Crit Care **2000**; 6:117–22.
34. Rossi M, Sganga G, Mazzone M, et al. Cardiopulmonary bypass in man: role of the intestine in a self-limiting inflammatory response with demonstrable bacterial translocation. Ann Thorac Surg **2004**; 77:612–8.
35. Salsano A, Giacobbe DR, Sportelli E, et al. Risk factors for infections due to carbapenem-resistant *Klebsiella pneumoniae* after open heart surgery. Interact Cardiovasc Thorac Surg **2016**; 23:762–8.
36. Guillamet CV, Vazquez R, Micek ST, et al. Development and validation of a clinical prediction rule for candidemia in hospitalized patients with severe sepsis and septic shock. J Crit Care **2015**; 30:715–20.
37. Bartoletti M, Rinaldi M, Pasquini Z, et al. Risk factors for candidemia in hospitalized patients with liver cirrhosis: a multicenter case-control-control study. Clin Microbiol Infect. **In press**.
38. Poissy J, Damonti L, Bignon A, et al; FUNGINOS; Allfun French Study Groups. Risk factors for candidemia: a prospective matched case-control study. Crit Care **2020**; 24:109.
39. Zhai B, Ola M, Rolling T, et al. High-resolution mycobiota analysis reveals dynamic intestinal translocation preceding invasive candidiasis. Nat Med **2020**; 26:59–64.
40. Andes DR, Safdar N, Baddley JW, et al; Mycoses Study Group. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis **2012**; 54:1110–22.